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For: TREATMENT FOR RENAL FIBROSIS

Attorney Docket No.: 85189-5500

SUBMISSION OF CERTIFIED PRIORITY DOCUMENT

Commissioner for Patents
P.O. Box 1450
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Sir:

Applicants have claimed priority under 35 U.S.C. § 119 of Israeli Application Nos. IL14336 filed on May 24, 2001 in Israel. In support of this claim, a certified copy of said applications is submitted herewith.

No fee or certification is believed to be due for this submission. Should any fees be required, however, please charge such fees to **Winston & Strawn LLP** Deposit Account No. 50-1814.

Respectfully submitted,

Date: 5/10/04

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Enclosures

(212) 294-3311

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PATENT LAW, 5727 - 1967

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בקשה לפטנט
Application for Patent

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TREATMENT OF RENAL FIBROSIS

מבקש בזאת כי ינתן לי עליה פטנט
hereby apply for a patent to be granted to me in respect thereof.

*בקשת חלוקה - Application of Division	*בקשת פטנט מוסף - Application for Patent Addition	*דרישה דין קדימה Priority Claim		
מבקשת פטנט From Application	*לבקשה/לפטנט to Patent/Appl.	מספר/סימן Number/Mark	תאריך Date	מדינת האגוד Convention Country
מס' No.....	מס' No.			
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חתימת המבקש Signature of Applicant ...licants, ...b		היום 23 בחודש מאי שנת 2001 This 23 of May of the year 2001		

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TREATMENT OF RENAL FIBROSIS

COLL-014

TREATMENT OF RENAL FIBROSIS

FIELD OF THE INVENTION

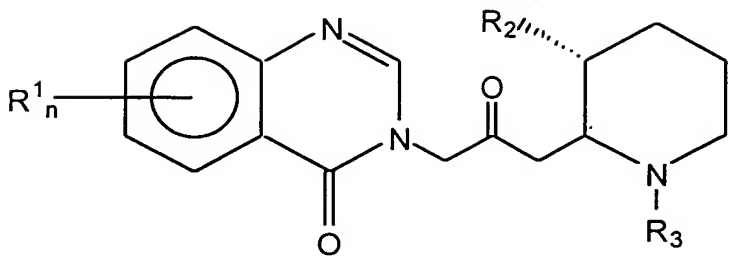
The present invention relates to compositions containing quinazolinones. More particularly, the present invention relates to a composition for treatment renal fibrosis, comprising as active ingredient therein a quinazolinone derivative as herein defined.

BACKGROUND OF THE INVENTION

Halofuginone

US Patent 3,320,124, disclosed and claimed a method for treating coccidiosis with quinazolinone derivatives. Halofuginone, otherwise known as 7-bromo-6-chloro-3-[3-(3-hydroxy-2-piperidinyl)-2-oxopropyl]-4(3H)-quinazolinone (one of the quinazolinone derivative), was first described and claimed in said patent by American Cyanamid company, and was the preferred compound taught by said patent and the one commercialized from among derivatives described and claimed therein. Subsequently, US patents 4,824,847; 4,855,299; 4,861,758 and 5,215,993 all relate to the coccidiocidal properties of Halofuginone.

More recently, it was disclosed in U.S. Patent No. 5,449,678 that these quinazolinone derivatives are unexpectedly useful for the treatment of a fibrotic condition. This disclosure provides compositions of a specific inhibitor comprising a therapeutically effective amount of a pharmaceutically active compound of the formula:



wherein: n=1-2

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl. Pharmaceutically acceptable salts thereof are also included. Of this group of compounds, Halofuginone has been found to be particularly effective for such treatment.

U.S. Patent No. 5,449,678 discloses that these compounds are effective in the treatment of fibrotic conditions such as scleroderma and GVHD. U.S. Patent No. 5,891,879 further discloses that these compounds are effective in treating restenosis. The two former conditions are associated with excessive collagen deposition, which can be inhibited by Halofuginone. Restenosis is characterized by smooth muscle cell proliferation and extracellular matrix accumulation within the lumen of affected blood vessels in response to a vascular injury [Choi *et al.*, *Arch. Surg.*, **130**:257-261, 1995]. One hallmark of

such smooth muscle cell proliferation is a phenotypic alteration, from the normal contractile phenotype to a synthetic one. Type I collagen has been shown to support such a phenotypic alteration, which can be blocked by Halofuginone [Choi *et al.*, *Arch. Surg.*, **130**: 257-261, 1995; U.S. Patent No. 5,449,678].

Notably, the *in vitro* action of Halofuginone does not always predict its *in vivo* effects. For example, Halofuginone inhibits the synthesis of collagen type I in bone chrondrocytes *in vitro*, as demonstrated in U.S. Patent No. 5,449,678. However, chickens treated with Halofuginone were not reported to have an increased rate of bone breakage, indicating that the effect is not seen *in vivo*.

In addition, even though halofuginone inhibits of collagen synthesis by fibroblasts in vitro, it promotes wound healing in vivo (WO 01/17531). Thus, the exact behavior of Halofuginone *in vivo* cannot always be accurately predicted from *in vitro* studies.

Chronic renal failure

The progression of chronic renal failure (CRF) represents one of the bigger challenges in nephrology as it leads to a large number of patients reaching end stage renal failure and requiring long-term dialysis treatment.

Many renal diseases progress to end stage renal failure with glomerular sclerosis and/or medullar fibrosis independent of the initial pathogenesis mechanism. This suggests that progressive renal diseases may exhibit a

common destructive pathway that leads to focal and eventually diffuse glomerulosclerosis and chronic tubuloinsterstitial disease.

Since there is a possibility that direct inhibition of renal fibrosis, which is considered the final common pathway, will attenuate the development of chronic renal failure (CRF), therapeutic antifibrotic strategies should be targeted to reduce or eliminate this process.

Chronic kidney diseases are characterized by the accumulation of extracellular matrix (ECM) in glomeruli and interstitium which lead finally to renal fibrosis and chronic renal failure [Klahr S. et Al., N Engl J Med 318:1657-1666,1988].

The pathogenesis of renal fibrosis includes the formation of fibrotic tissue in the kidney. The formation of fibrotic tissue is characterized by the deposition of abnormally large amounts of collagen. Following kidney injury (the term includes physical injury, toxic, vascular) mesangial cells have the capacity to synthesize collagen types I and III, as opposed to the exclusive presence of type IV collagen in healthy glomeruli (Trai et al., 1994). In vitro, mesangial cells have the capacity to release matrix metallo-proteinase (MMPr) capable of degrading collagen IV, but not collagen I and III (Daniel et. al. 1998). The synthesis of collagen is also involved in a number of other pathological conditions. For example, clinical conditions and disorders associated with primary or secondary fibrosis, such as systemic sclerosis, graft-versus-host

disease (GVHD), pulmonary and hepatic fibrosis and a large variety of autoimmune disorders, are distinguished by excessive production of connective tissue, which results in the destruction of normal tissue architecture and function. These diseases can best be interpreted in terms of perturbations in cellular functions, a major manifestation of which is excessive collagen synthesis and deposition. The crucial role of collagen in fibrosis has prompted attempts to develop drugs that inhibit its accumulation [K.I. Kivirikko, *Annals of Medicine*, Vol. 25, pp. 113-126 (1993)].

Glomerular sclerosis is characterized by replacement of the functional glomeruli by connective tissue mainly through expansion of the mesangial cells and deposition of ECM.

Interstitial fibrosis is characterized by the destruction of renal tubules and interstitial capillaries as well as by the accumulation of extracellular matrix proteins [M. Fukagawa et. al. Nephrol Dial Transplant (1999) 14:2793-2795].

Fibrosis is believed to result from excessive synthesis of ECM and a concomitant decrease in its breakdown.

Focal and segmental glomerulosclerosis (FSGS) is the histological description of a form of glomerular injury that is usually associated with proteinuria and progressive loss of renal function [see H.G. Rennke and P.S. Klein,

"Pathogenesis and Significance of nonprimary Focal and segmental Glomerulosclerosis" Am. J. Kid. Dis. Vol. 13, pp.443-46 (1989)].

Originally, FSGS was described in nephrotic patients who had died with end stage renal failure. In more recent years, FSGS has been identified as a final common pathway in the glomerulus in a number of human systemic and renal diseases. These include processes such as normal aging and diabetic nephropathy. The pathologic lesion of FSGS can result from a variety of seemingly unrelated injurious stimuli, leading through extracellular matrix deposition and glomerulosclerosis to renal demise long after the termination of the initial injury.

Such drugs can act by modulating the synthesis of the procollagen polypeptide chains, or by inhibiting specific post-translational events, which will lead either to reduced formation of extra-cellular collagen fibers or to an accumulation of fibers with altered properties. Unfortunately, only a few inhibitors of collagen synthesis are available, despite the importance of this protein in sustaining tissue integrity and its involvement in various disorders.

For example, cytotoxic drugs have been used in an attempt to slow the proliferation of collagen-producing fibroblasts [J.A. Casas, *et al.*, *Ann. Rhem. Dis.*, **46**: 763, 1987], such as colchicine, which slows collagen secretion into the extracellular matrix [D. Kershenobich, *et al., N. Engl. J. Med.,* **318**:1709, 1988], as well as inhibitors of key collagen metabolism enzymes [K. Karvonen,

et al., *J. Biol Chem.*, **265**: 8414, 1990; C.J. Cunliffe, *et al.*, *J. Med. Chem.*, **35**:2652, 1992].

Unfortunately, none of these inhibitors are collagen-type specific. Also, there are serious concerns about the toxic consequences of interfering with biosynthesis of other vital collagenous molecules, such as Clq in the classical complement pathway, acetylcholine esterase of the neuro-muscular junction endplate, conglutinin and renal surfactant apoprotein.

Other drugs which can inhibit collagen synthesis, such as nifedipine and phenytoin, inhibit synthesis of other proteins as well, thereby non-specifically blocking the collagen biosynthetic pathway [T. Salo, *et al.*, *J. Oral Pathol. Med.*, **19**: 404 ,1990].

Collagen cross-linking inhibitors, such as β-amino-propionitrile, are also non-specific, although they can serve as useful anti-fibrotic agents. Their prolonged use causes lathritic syndrome and interferes with elastogenesis, since elastin, another fibrous connective tissue protein, is also cross-linked. In addition, the collagen cross-linking inhibitory effect is secondary, and collagen overproduction has to precede its degradation by collagenase. Thus, a type-specific inhibitor of the synthesis of collagen itself is clearly required as an anti-fibrotic agent.

The ability of Halofuginone, or other related quinazolinone derivative, to block or inhibit pathological processes related to renal fibrosis, has only been shown in U.S. 5,998,442. That patent disclosed a pharmaceutical composition

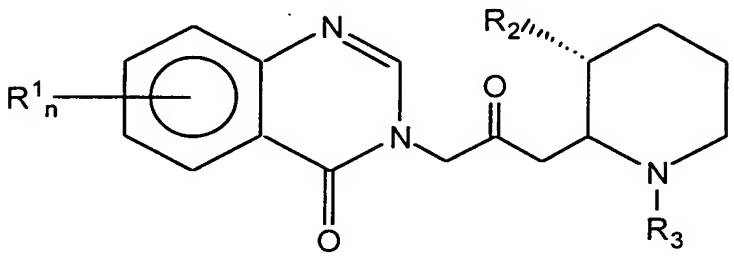
containing quinazolinone derivatives for attenuation of Mesangial Cells proliferation wherein all the examples were tested *in vitro*. Moreover, the strong fibrotic process in the tubulointerstitial compartments that characterizes the renal fibrosis disease does not involve any mesangial cell proliferation.

Nothing in the prior art taught or suggested that Halofuginone would be useful in the treatment of renal fibrosis *in vivo*. It was clearly impossible to anticipate that halofuginone would be useful to prevent progression of renal disease to end-stage renal failure. Thus, the ability of Halofuginone and related compounds to slow or halt progression of fibrosis in the kidneys is both novel and non obvious.

SUMMARY OF THE INVENTION

Unexpectedly, it has been found, as described below, that pharmaceutical compositions containing quinazolinone derivatives, especially Halofuginone, can also inhibit the pathophysiological processes of renal fibrosis *in vivo*, including the effect on both the glomeruli and the tubuli interstitial compartments, possibly by inhibiting collagen type I synthesis, although other mechanisms can also be responsible. While inhibition of collagen type I synthesis is proposed as one plausible mechanism, it is not desired to be limited to a single mechanism, nor is it necessary since the *in vivo* data presented below clearly demonstrate the efficacy of Halofuginone as an inhibitor of renal fibrosis *in vivo*.

According to the present invention, there is provided a composition for treating renal fibrosis, comprising a pharmaceutically effective amount of a compound in combination with a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:



wherein: n=1-2

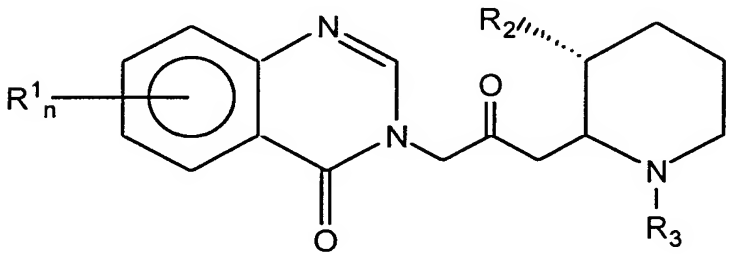
R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl and pharmaceutically acceptable salts thereof.

According to further preferred embodiments of the present invention, the compound is preferably Halofuginone.

According to another embodiment of the present invention, there is provided a method of manufacturing a medicament for treating renal fibrosis, including the step of placing a pharmaceutically effective amount of a compound in a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:

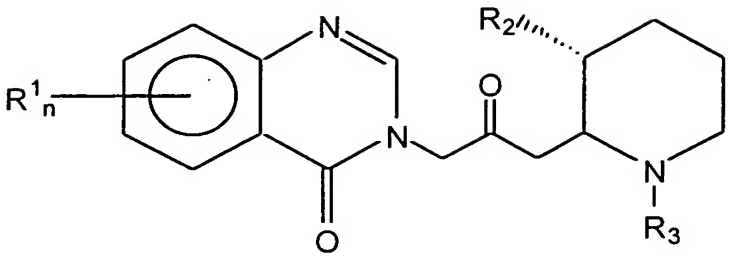


wherein: n=1-2

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl and pharmaceutically acceptable salts thereof.

According to yet another embodiment of the present invention, there is provided a method for the treatment of renal fibrosis in a subject, including the step of administering a pharmaceutically effective amount of a compound having a formula:



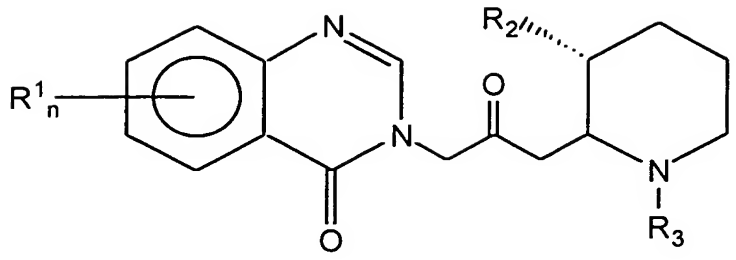
wherein: n=1-2

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl, and pharmaceutically acceptable salts thereof.

The renal fibrosis can be primary or secondary. Primary renal fibrosis is related to a condition that affects the kidney without being the result of some other disease or disorder, whereas secondary renal fibrosis is the result of some underlying pathology. The secondary condition may be caused by high hypertension, diabetes complications, autoimmune disease, and other disorders.

The present invention further provides a method for preventing renal fibrosis from progressing to end stage renal failure comprising administering to a subject in need thereof a therapeutically effective amount of compound in a pharmaceutically acceptable carrier, said compound being a member of a group having the formula:



wherein: n=1-2

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl, and pharmaceutically acceptable salts thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings, wherein:

FIG. 1: is a graph of the effect of Halofuginone on systolic blood pressure (SBP) in rats.

FIG. 2: is a graph of the effect of Halofuginone on protein concentration in rat urine.

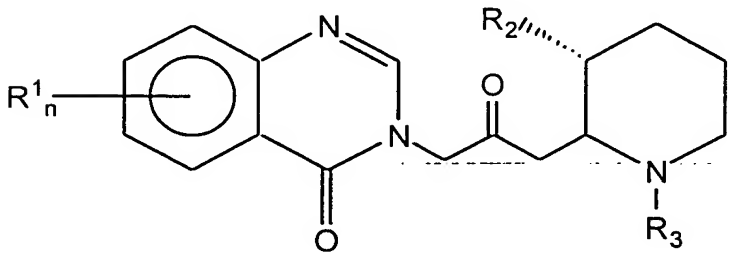
FIG. 3: is a graph of the effect of Halofuginone on body weight in rats.

FIG 4: is a graph of the effect of Halofuginone on creatinine clearance (CCR)

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Unexpectedly, it has been found, as described in the examples herein below, that Halofuginone can inhibit the pathological process of renal fibrosis *in vivo,* possibly by inhibiting collagen type I synthesis, although another mechanisms could also be responsible. Indeed irrespective of the specific mechanism, the data presented below clearly demonstrate the efficacy of Halofuginone *in vivo* for inhibition of the pathological progression of renal fibrosis.

According to the present invention, there is provided a composition for treating renal fibrosis, comprising a pharmaceutically effective amount of a compound in combination with a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:



wherein: n=1-2

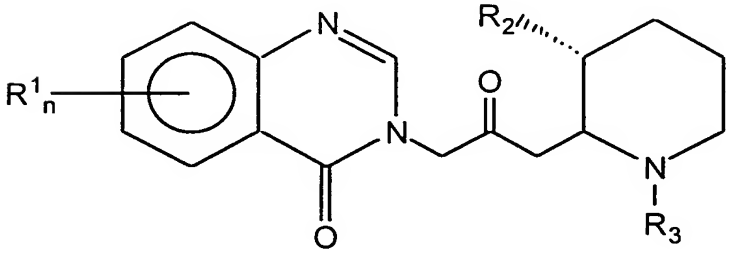
R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl and pharmaceutically acceptable salts thereof.

According to further preferred embodiments of the present invention, the compound is preferably Halofuginone.

According to another embodiment of the present invention, there is provided a method of manufacturing a medicament for treating renal fibrosis, including the step of placing a pharmaceutically effective amount of a compound in a pharmaceutically acceptable carrier, the compound being a member of a group having a formula:

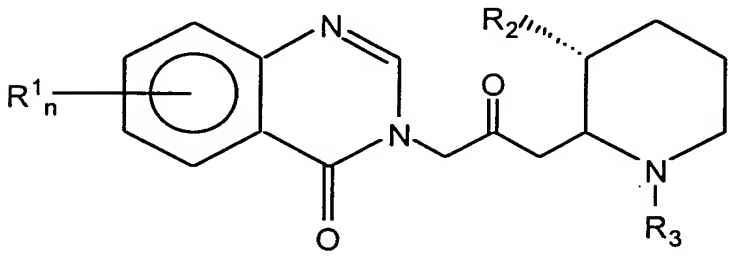


wherein: n=1-2

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl and pharmaceutically acceptable salts thereof.

According to yet another embodiment of the present invention, there is provided a method for the treatment of renal fibrosis in a subject, including the step of administering a pharmaceutically effective amount of a compound having a formula:



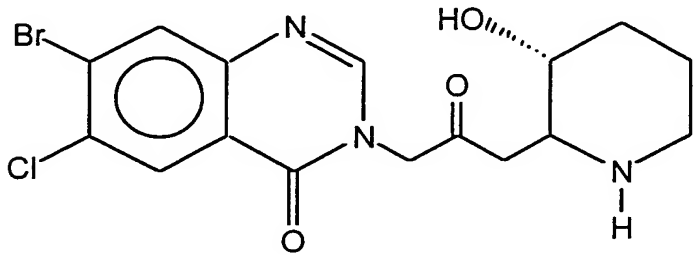
wherein: n=1-2

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl, and pharmaceutically acceptable salts thereof.

The renal fibrosis can be primary or secondary. The secondary condition may be caused by high hypertension, diabetes complications, autoimmune disease, and other underlying disorders and conditions.

According to further preferred embodiments of the present invention, the compound is preferably Halofuginone. Hereinafter, the term "Halofuginone" is defined as a compound having the formula:



and pharmaceutically acceptable salts thereof. The composition preferably includes a pharmaceutically acceptable carrier for the compound.

Hereinafter, the term "subject" refers to the human or animal to whom Halofuginone was administered. The term "patient" refers to human subjects.

The term "treatment" includes both substantially preventing the process of renal fibrosis from starting and slowing or halting the progression of renal fibrosis once it has arisen. The term "renal fibrosis" refers to any fibrotic condition in the kidneys of the subject.

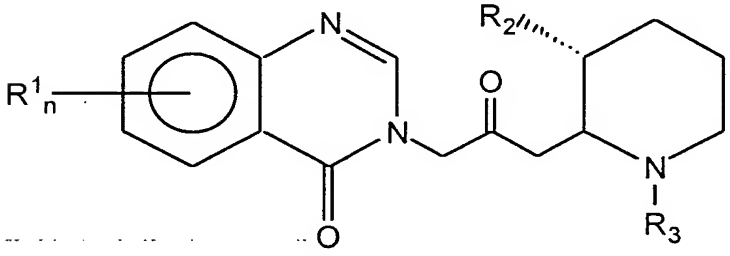
Hereinafter, the term "oral administration" includes, but is not limited to administration by mouth for absorption through the gastrointestinal tract, buccal administration and sublingual administration.

Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, sachets, capsules or tablets. Thickeners, diluents, flavorings, dispersing aids, emulsifiers, binders or preservatives may be desirable.

The term "parenteral administration" includes, but is not limited to, administration by intravenous drip or bolus injection, subcutaneous, or intra muscular injection.

Formulations for parenteral administration may include but are not limited to sterile aqueous solutions which may also contain buffers, diluents and other suitable additives.

Although the specific quinazolinone derivative "Halofuginone" is referred to throughout the specification, it is understood that other quinazolinone derivatives may be used in its place, these derivatives having the formula:



wherein: n=1-2

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl, and pharmaceutically acceptable salts thereof.

Compounds which are intended for the inhibition of renal fibrosis must be tested an *in vivo* model for their ability to slow or halt the pathological process leading to deposition of fibrotic tissue.

Such experiments were conducted for the collagen type I synthesis inhibitor Halofuginone, as described in greater detail in the Examples below.

Renal fibrosis has been induced in rats by undergo renal mass reduction (RMR) or sham operation. The present invention may be more readily understood with reference to the following illustrative examples and figures.

While the invention will now be described in connection with certain preferred embodiments in the following figures and examples so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following figures and examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and

readily understood description of formulation procedures as well as of the principles and conceptual aspects of the invention.

EXAMPLE 1

Solution of Halofuginone was prepared by dissolution of powder of Halofuginone hydrobromide in aqueous media containing suitable buffer.

Male Wistar rats (weighing 300±30g at the start of the experiment) were used in this study and allowed to acclimatize to their environment for one week. Rats were assigned to undergo renal mass reduction (RMR) or sham operation, under anesthesia with intraperitoneal injection of pentobarbital (30mg/kg body weight). RMR was performed by ligature of 2 of 3 major branches of the left renal artery and right nephrectomy in the same session. Sham rats undergo exposure of the kidneys and removal of the peri-renal fat, without undergoing RMR. After 24 hours recovery of the rats were assigned to one of the following groups:

1) Group I: RMR rats, oral gavage with halofuginone 0.2mg/kg/day started 24 hours post surgery.
2) Group II: RMR rats, oral gavage with normal saline daily, started 24 hours post surgery.
3) Group III: age matched, sham operated rats served as the controls.

All animals were allowed free access to a standard diet and water ad libitum.

Every week, systolic blood pressure was measured by tail cuff manometer and urine samples were collected individually in metabolic cages for determination of total protein, albumin, creatinine and urea. At sacrifice (10 weeks after RMR) blood was withdrawn from abdominal aorta for creatinine, albumin and cholesterol determinations, as well as Halofuginone levels.

Kidneys were removed and processed for in situ hybridization, immunohistochemistry and histological evaluation.

Light microscopy studies: specimens were fixed in 10% buffered formaldehyde and embedded in paraffin. Histological sections of 4-5μ thickness were stained with hematoxylin-eosin (HES), periodic acid Schiff (PAS) and Masson trichrome (light green).

A semi-quantitative score was used to evaluate the degree of glomerulosclerosis, mesangial expansion and proliferation and tubulo-interstitial changes.

A minimum of 60 glomeruli in each specimen was examined and the severity of the lesions was graded from 0 to +4. These results showed that even at a low dose Halofuginone was shown to have a beneficial effect on the kidneys, delaying the proteinuria as well as reducing the deterioration of creatinine clearance. Both phenomena suggest preservation of renal function.

These results showed that even at a low dose, Halofuginone reduces proteinuria as well as the severity of fibrosis in interstitial and glomerular renal structures in this 5/6NX rat model. Better preservation of renal function was observed in the Halo group, as shown in Table 1..

Table 1. THE EFFECT OF HALOFUGINONE ON 5/6 NEPHRECTOMY IN RATS: LIGHT MICROSCOPY (PRELIMINARY RESULTS)

Halofuginone Group I (rat)	Glomerulus		Tubules	Interstitium	
	proliferation	sclerosis		Fibrosis	Infiltration
1	Mild	0	Normal	-	-
2	Moderate	0	Few atrophic	+	+
3	Mild	0	Few atrophic	-	-
4	Mild	0	Few atrophic	-	-
5	Mild	0	Few atrophic	-	+
6	Moderate	0	Few atrophic	+	++

Control Group II	Glomerulus		Tubules	Interstitium	
	proliferation	sclerosis		Fibrosis	Infiltration
1	Severe	1	Atrophic ++	++	+
2	Severe	1	Dilated++	-	+
3	Severe	1	Dilated-Atrophic ++	++	++
4	Severe	1	Atrophic++	++	+
5	Moderate to severe	1	Atrophic+	++	++

In the presence of the severe hypertension the treated animals showed delay proteinuria reduced fibrosis and preservation of renal structure and function , plasma levels were formed to be around the level of detection (±1ng/ml).

These results suggest that even in less than optimal levels, Halofuginone does not prevent initiation of the pathological process, but does provide a beneficial effect on the kidneys.

EXAMPLE 2

Male Wistar rats (weighing 300±30g at the start of the experiment) are used. in this study. They were allowed to acclimatize to their environment for one week. Rats were assigned to undergo renal mass reduction (RMR) or Sham operation, under anesthesia with intraperitoneal injection of pentobarbital (30mg/kg body weight). RMR was performed by ligature of 2 of 3 major branches of the left renal artery and right nephrectomy in the same session. Sham rats have undergone exposition of the kidneys and removal of the peri-renal fat. After 24 hours recovery the rats were assigned to one of the following groups:

1) Group I: RMR rats, osmotic pump administration of halofuginone 0.2mg/kg/day started 24 hours post surgery.
2) Group II: RMR rats, osmotic pump administration of halofuginone 0.4mg/kg/day started 24 hours post surgery.
3) Group III: RMR rats, osmotic pump administration of normal saline daily, started 24 hours post surgery.
4) Group IV: age matched, sham operated rats served as the ablative controls.

All animals are allowed free access to a standard diet and water ad libitum. Every week, systolic blood pressure is measured by tail cuff manometry and urine samples are collected individually in metabolic cages for determination of total protein, albumin, creatinine and urea. At sacrifice (10 weeks after RMR)

blood is withdrawn from abdominal aorta for creatinine, albumin and cholesterol determinations.

EXAMPLE 3

Method of Treatment of Renal Fibrosis

As noted above, Halofuginone has been shown to be an effective inhibitor of renal fibrosis. The following example is an illustration only of a method of treating renal fibrosis with Halofuginone, and is not intended to be limiting.

The method includes the step of administering Halofuginone, in a pharmaceutically acceptable carrier as described above, to a subject to be treated. Halofuginone is administered according to an effective dosing methodology, preferably until a predefined endpoint is reached, such as the absence of further progression of renal fibrosis in the subject, the inhibition of renal fibrosis or the prevention of the formation of renal fibrosis.

Halofuginone can be administered to a subject in a number of ways, which are well known in the art. Hereinafter, the term "subject" refers to the human or lower animal to whom Halofuginone was administered. For example, administration may be done orally, or parenterally, for example by intravenous drip or bolus injection, subcutaneous, or intramuscular injection.

Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, sachets, capsules or tablets.

Thickeners, diluents, flavorings, dispersing aids, emulsifiers, preservatives or binders may be desirable.

Formulations for parenteral administration may include but are not limited to sterile aqueous solutions which may also contain buffers, diluents and other suitable additives.

Dosing is dependent on the severity of the symptoms and on the responsiveness of the subject to Halofuginone. The attending physician can easily determine optimum dosages, dosing methodologies and repetition rates.

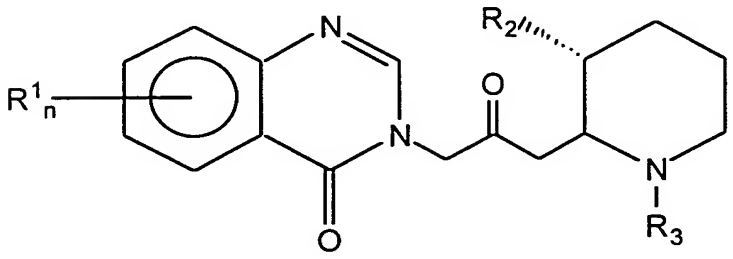
EXAMPLE 4

Method of Manufacture of a Medicament Containing Halofuginone

The following is an example of a method of manufacturing Halofuginone. First, Halofuginone is synthesized in accordance with good pharmaceutical manufacturing practice. Examples of methods of synthesizing Halofuginone, and related quinazolinone derivatives, are given in U.S. Patent No. 3,338,909. Next, Halofuginone is placed in a suitable pharmaceutical carrier, as described in Example 3 above, again in accordance with good pharmaceutical manufacturing practice.

Claims:

1. A composition for treating renal fibrosis, comprising a pharmaceutically effective amount of a compound in combination with a pharmaceutically acceptable carriers, said compound being a member of a group having a formula:



wherein: n=1-2

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

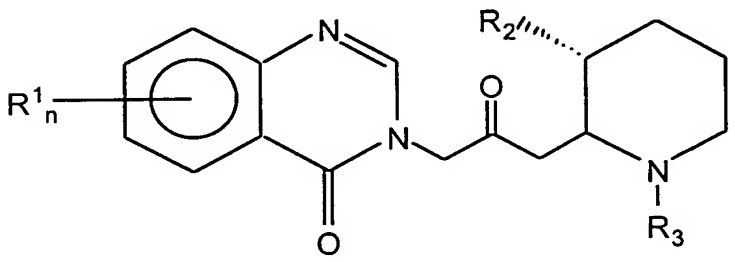
R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl, and pharmaceutically acceptable salts thereof.

2. The composition of claim 1, wherein said compound is Halofuginone.

3. The composition of claim 1 wherein said pharmaceutically acceptable carrier enables administration the composition orally or parenterally in form of

powder, granules, suspensions or solutions in water or non aqueous media, sachets, capsules or tablets.

4. A method for treating renal fibrosis in a subject, comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition comprising as an active ingredient a compound having the formula:



wherein: n=1-2

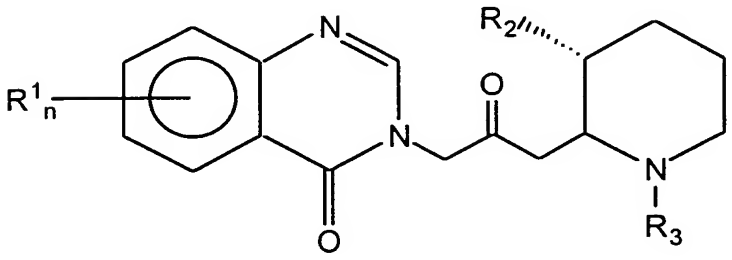
R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl, and pharmaceutically acceptable salts thereof.

5. The method of claim 4, wherein said compound is Halofuginone.

Claims:

1. A composition for treating renal fibrosis, comprising a pharmaceutically effective amount of a compound in combination with a pharmaceutically acceptable carriers, said compound being a member of a group having a formula:



wherein: n=1-2

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

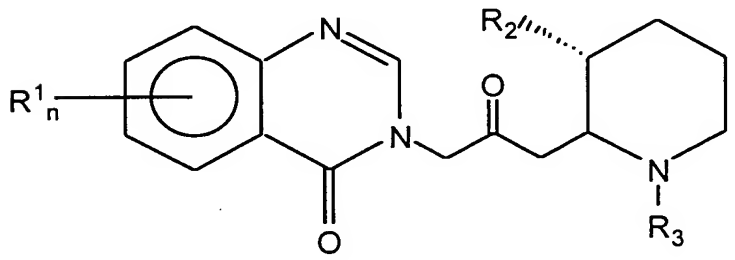
R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl, and pharmaceutically acceptable salts thereof.

2. The composition of claim 1, wherein said compound is Halofuginone.

3. The composition of claim 1 wherein said pharmaceutically acceptable carrier enables administration the composition orally or parenterally in form of

powder, granules, suspensions or solutions in water or non aqueous media, sachets, capsules or tablets.

4. A method for treating renal fibrosis in a subject, comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition comprising as an active ingredient a compound having the formula:



wherein: n=1-2

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl, and pharmaceutically acceptable salts thereof.

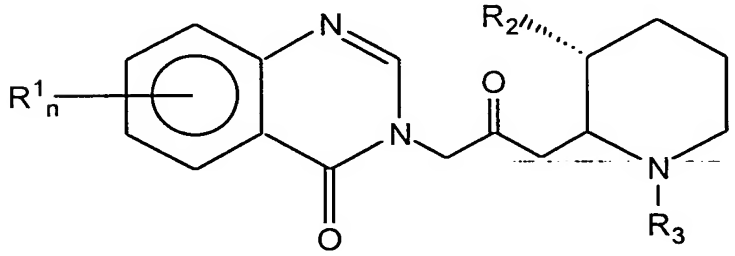
5. The method of claim 4, wherein said compound is Halofuginone.

6. The method of claim 4, wherein said pharmaceutical composition is suitable for administration orally or parenterally in the form of powder, granules, suspensions or solutions in water or non aqueous media, sachets, capsules or tablets.

7. The method of claim 4, wherein the renal fibrosis condition is primary or secondary.

8. The method of claim 7 wherein the secondary condition is caused by hypertension, diabetic complications, or autoimmune diseases.

9. A method for preventing renal fibrosis from progressing to end stage renal failure comprising administering to a subject in need thereof a therapeutically effective amount of compound in a pharmaceutically acceptable carrier, said compound being a member of a group having the formula:



wherein: n=1-2

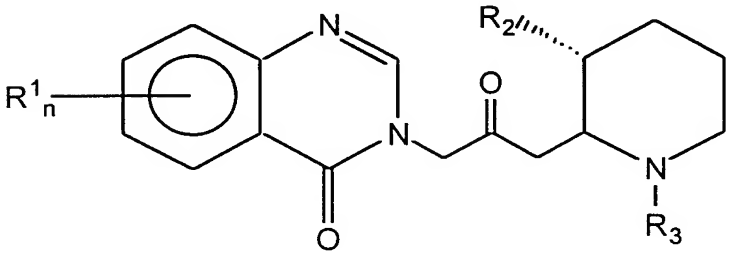
R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl, and pharmaceutically acceptable salts thereof.

10. The method of claim 9, wherein said compound is Halofuginone.

11. The method of claim 9, wherein said pharmaceutically acceptable carrier enables administration the composition orally or parenterally in the form of powder, granules, suspensions or solutions in water or non aqueous media, sachets, capsules or tablets.

12. Use of a compound being a member of the group having the formula:



wherein: n=1-2

R_1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy; R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl, and pharmaceutically

acceptable salts thereof, for preparing a pharmaceutical composition for treating renal fibrosis, substantially as described in the specification.

13. Use according to claim 12, wherein the compound is Halofuginone.

14. Use according to claim 12, wherein said medicament is suitable for administration orally or parenterally in the form of powder, granules, suspensions or solutions in water or non aqueous media, sachets, capsules or tablets.

For the applicants

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ABSTRACT

The present invention relates to compositions containing quinazolinones. More particularly, the present invention relates to a composition for treatment renal fibrosis, comprising as active ingredient a quinazolinone derivative as herein defined. The currently preferred embodiment is halofuginone, which is now shown to slow or prevent progression of renal fibrosis in vivo.

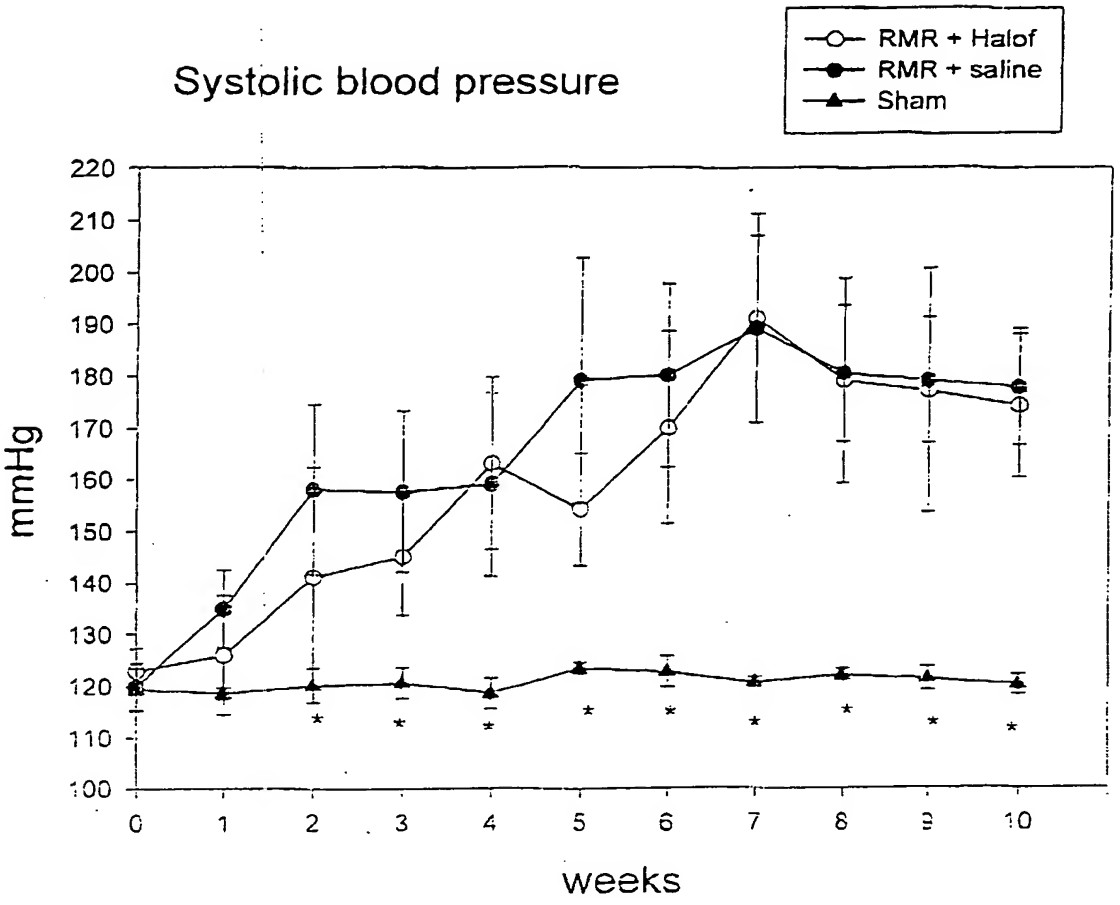

Fig.1. Time course of systolic blood pressure (SBP) in untreated and halofuginone (halof) - treated RMR rats and in comtrol sham operated rats. * Significantly lower ($p < 0.01$) than both RMR groups

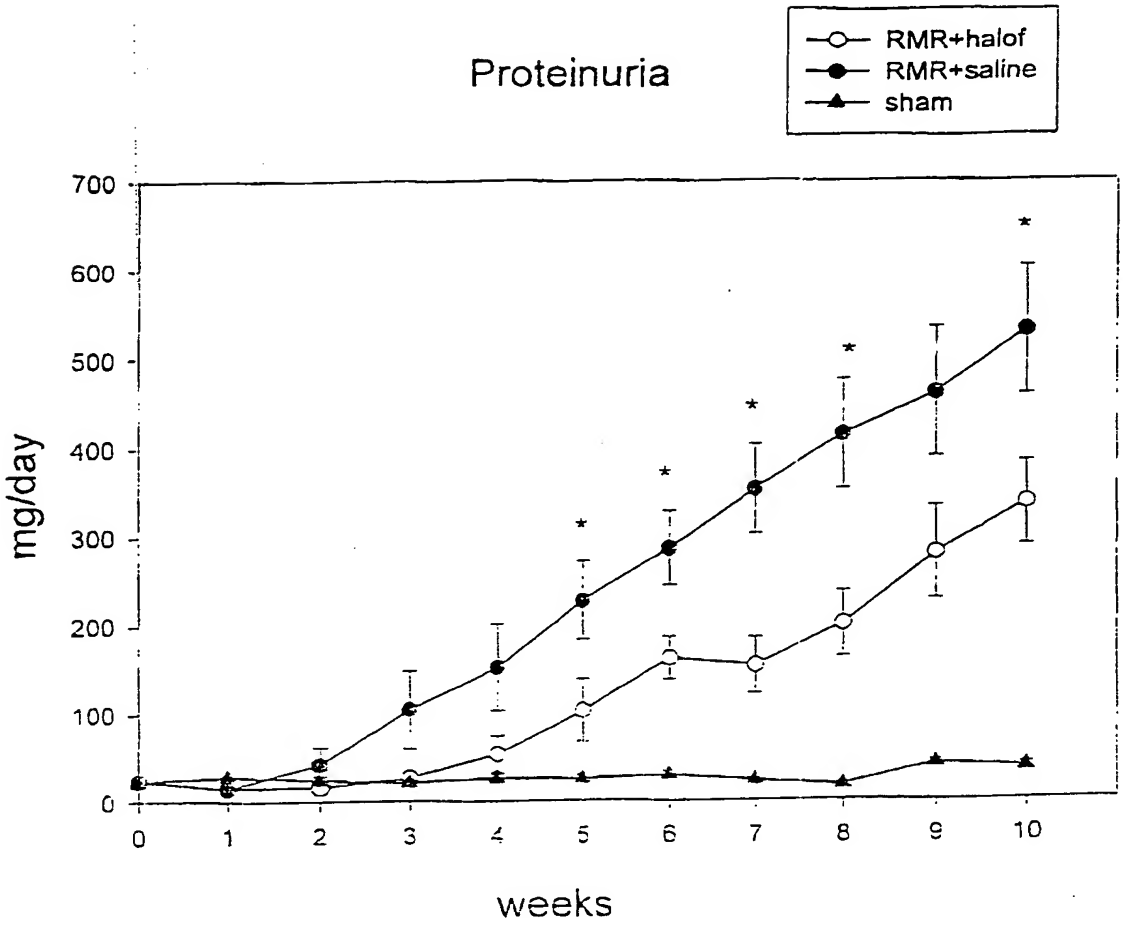

Fig.2.Time course of proteinuria in untreated and halofuginone(halof)-treated RMR rats and in control sham operated rats
* Significantly higher ($p<0.05$) than halof-treated and sham groups

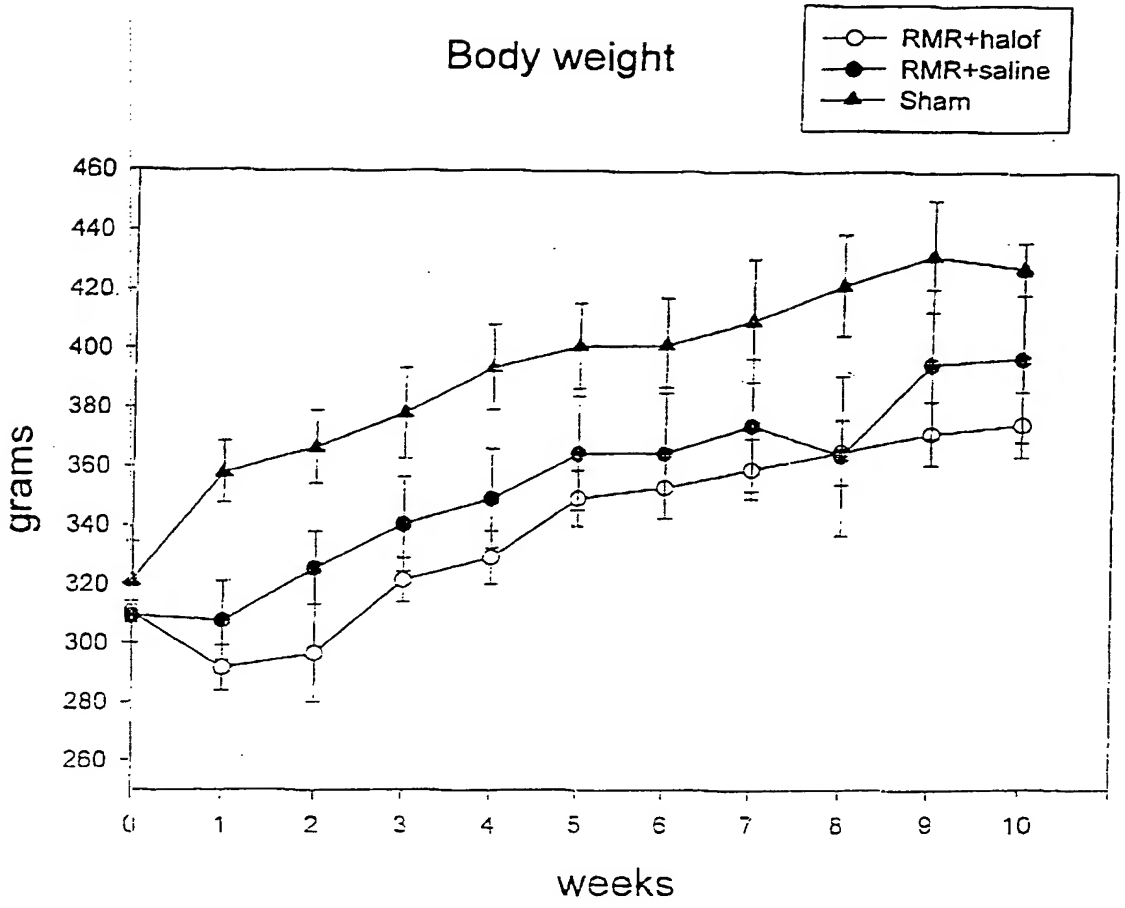

Fig.3. Time course of body weight in untreated and halofuginone (halof) - treated RMR rats and in control sham operated rats

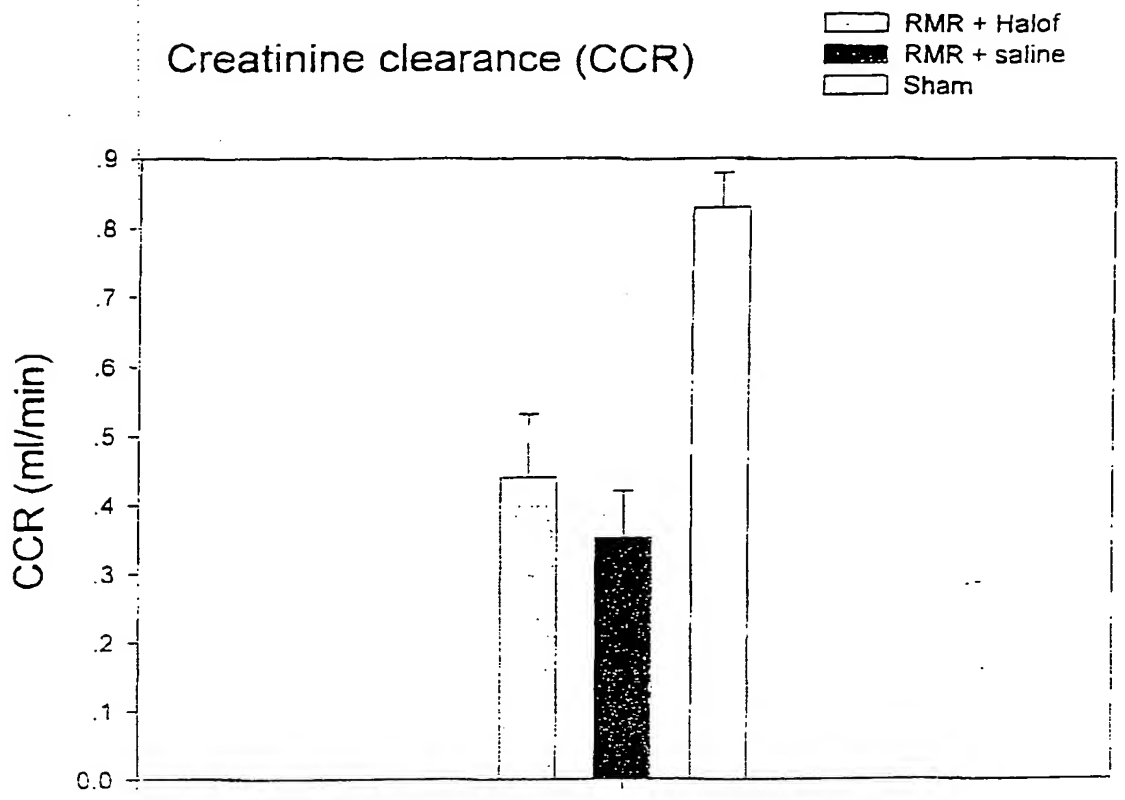

Fig 4: Creatinine clearance in untreated and halofuginone treated RMR rats (10 weeks post RMR)